Specialty Conference

Moderator

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Discussants

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Infectious Disease Emergencies

PART V:

Patients Presenting with Localized Infections

PHYLLIS OILL, MD:* This is the fifth and final part of the symposium on Infectious Disease Emergencies. The discussions will deal with emergent and semi-emergent localized infections. First, Dr. Montgomerie will discuss soft tissue infections. The next discussant, Dr. William Cryan, will address himself to the topic of septic arthritis, and finally, Dr. John Edwards will discuss emergency eye infections.

Soft Tissue Infections

JOHN MONTGOMERIE, MD:† Inasmuch as this symposium deals with infectious diseases emergencies, only those serious and potentially life-threatening soft tissue infections will be discussed. Successful management of most of these infections depends on early diagnosis, usually by clinical signs alone. Table V-1 has been compiled to aid in the differential diagnosis of the first five soft tissue infections presented (clostridial myonecrosis, streptococcal and staphylococcal myositis, synergistic necrotizing cellulitis, necrotizing fasciitis, progressive bacterial synergistic gangrene). Salient features of decubitus ulcers with sepsis, human and animal bites, and serious furunculosis and cellulitis are also discussed.

Clostridial Myonecrosis (Gas Gangrene)

Clostridial myonecrosis or gas gangrene is a rapidly progressive infection associated with muscle necrosis, but relatively little inflammatory reaction. Although the highest prevalence of gas gangrene has been associated with war wounds, the disease also occurs in civilian practice following trauma, intraabdominal surgical procedures, especially cholecystectomy and intestinal resections, septic abortion and limb amputations. Patients with diabetes mellitus, certain types of neoplastic disease and disorders of the intestine in which there is appreciable necrosis of tissue are particularly predisposed to this infection.[1]

The etiologic agents are various histotoxic clostridia (Clostridium perfringens, C. novyi, C. septicum, C. histolyticum, C. bifermentans and C. fallax), with the most common pathogen being C. perfringens.[2] An individual lesion may yield more than one species. The toxins elabor-

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ABBREVIATIONS USED IN TEXT
GC = gonococcal
RA = rheumatoid arthritis

ated by these clostridia are, in part, responsible for the syndromes of gas gangrene.[2] Alpha toxin, a lecithinase, is the principal tissue-destroying, hemolytic and "lethal" toxin. Invasion of the blood stream by toxigenic clostridia rarely occurs as a complication of myonecrosis; however, in some patients, clostridial bacteremia leads to rapid and massive hemolysis as a result of the lecithinases.[1] Although the activities of some of the other toxins have also been defined, the precise cause of the systemic "toxicity" of this disease is still unclear.

The incubation period of gas gangrene is usually short, almost always less than three days and in most cases less than 24 hours.[2] The infection manifests itself with the sudden onset of pain in the region of the wound. The patient appears severely ill, pale and sweaty, and may be delirious, maniacal or apathetic.[1] Classically, there may be a peculiar period of great intellectual clarity, complete appreciation of the gravity of the circumstances, and a profound and distressing terror of impending death.[2] There is a pronounced rise in the pulse rate, but as a rule only a slight elevation in temperature, rarely to more than 100°F. After progression of signs and symptoms, a thin brownish exudate with a "mousey" odor begins to ooze from the wound. Crepitance may or may not be observed and gas is most easily detected on x-ray studies. It should be noted, however, that myositis may be present without gas. A bronze discoloration starts at the edge of the wound and progresses outward. Blebs or bullae filled with purplish fluid may appear, and by this time the patient may be anuric and in irreversible vascular collapse.[3]

Examination of the muscle by incision initially discloses only edema and pallor. As the infection progresses there is loss of contractility, absence of bleeding from the cut surface, and an increased reddening of the muscle from its normal color. Gas is present between the muscle fibers. Gram stain of the involved muscle shows large, Gram-positive or Gram-variable bacilli, but very few leukocytes.[3] Anaerobic cultures of this material should be sent to the laboratory for confirmation of the presence of clostridia. Smears of the superficial exudate from the wound may show a mixed bacterial flora due to contamination and may be misleading. Therefore, when gas gangrene is suspected, incision down to the muscle is necessary for direct observation, Gram stain and culture of muscle fibers.

TABLE V-1.—*Differential Diagnosis of Serious Soft Tissue Infections**

	Clostridial Myonecrosis	*Streptococcal Myositis*	*Synergistic Necrotizing Cellulitis*	*Necrotizing Fasciitis*	*Progressive Bacterial Synergistic Gangrene*
Incubation ..	18 hours to 3 days	3 to 4 days	3 to 14 days	1 to 4 days	10 to 14 days
Onset	Sudden	Gradual	Sudden	Sudden	Gradual
Toxemia	Marked	Marked after some time	Marked	Moderate to marked	Mild
Pain	Severe	Usually severe	Severe	Minimal; eventually hypoesthesia	Very marked
Exudate	Usually profuse, serosanguinous "mousey odor"	Very profuse, seropurulent	"Dishwater pus," foul smelling	Serosanguinous	Nil or slight
Gas	Rarely pronounced, except terminally	Present, not pronounced	Not pronounced, present in 25 percent of cases	Usually not present	Usually not present
Muscle	Edema, pallor to deep reddening; nonviable	Little change, but edema; viable	Moderate change, viable	Viable	No change
Skin	Tense, often white	Tense, often with coppery tinge	Discrete bluish-gray necrosis with areas of normal skin	Tense, pale red cellulitis	Fiery red cellulitis often purplish zone
Mortality ...	15 to 30 percent	5 to 10 percent	75 percent	30 percent	High

*Modified from Finegold SM, Bartlett, JG, Chow AW, et al: Management of anaerobic infections. Ann Intern Med 83:375-389, Sep 1975.

Additionally, the diagnosis of gas gangrene cannot be made simply by showing the presence of gas in tissues. A variety of other microorganisms (coliforms, anaerobic streptococci and bacteroides) may produce infections in which gas is shown present.[1] Crepitant cellulitis may be differentiated from gas gangrene by a more gradual onset of symptoms, a polymicrobial cause and involvement of epifascial soft tissues only.

Treatment must be prompt and vigorous, and complete surgical removal of all infected tissue is the only therapeutic modality proved to be unequivocally effective.[1,2,4] Antimicrobial therapy with penicillin G (10 to 20 million units per day in divided doses) is recommended to prevent blood stream invasion and to suppress further spread of infection. Chloramphenicol (4 grams per day in divided doses) is the alternative drug in penicillin-allergic patients. General supportive measures should include therapy with intravenously given fluids and blood, use of additional modalities to counteract the shock state and treatment with peritoneal dialysis or hemodialysis when renal failure is present. Hyperbaric oxygen has been advocated by some[5,6] as a dramatically successful mode of therapy that should even take precedence over immediate surgical management. The main advantage of hyperbaric oxygen therapy appears to be that it allows time for suitable medical resuscitation of the patient and better demarcation between necrotic and viable tissue before extensive surgical debridement is undertaken. If a suitable hyperbaric chamber is not locally available, it is probably unwise to delay surgical extirpation. The effectiveness of antitoxin therapy is unclear, but this should receive serious consideration when therapy with hyperbaric oxygen is not available.[1] The suggested dose of commercially available polyvalent antitoxin is 75,000 units given intravenously and repeated every six hours if necessary. Mortality in clostridial gas gangrene, despite vigorous therapy, ranges from 15 to 30 percent.[1,7]

Streptococcal and Staphylococcal Myositis

Streptococcal Myositis

This disease is characterized by severe local pain, generalized toxemia, discoloration, edema and crepitation of muscle.[8] It occurs in persons who have sustained traumatic wounds.

Streptococcol myositis may be due to anaerobic as well as aerobic streptococci (Streptococcus pyogenes, Streptococcus viridans), often in association with Staphylococcus aureus.[9]

The incubation period is approximately two to four days with a subacute or insidious onset. There is severe local pain with pronounced edema. A profuse, seropurulent discharge with a foul odor is generally present. There may be bleb formation and gangrene of the overlying skin. The skin is tense and can have a coppery tinge.[7] The muscle is edematous, but still viable and gas is apparent in the wound.[8]

The most important means of making the diagnosis is by direct examination of the muscle at operation. This is necessary in order to differentiate this disease from clostridial myonecrosis. This is usually possible by the more pronounced cutaneous reaction in the former, the discolored but still viable muscle, the foul odor and the presence of cocci on Gram stain of the fluid.[8]

Treatment requires incision and drainage of involved fascia and muscle groups. Concomittantly, antibiotic therapy is instituted with penicillin G (10 to 20 million units per day in divided doses) as the drug of choice. Mortality is 5 to 10 percent.[7]

Staphylococcal Myositis (Spontaneous Bacterial Myositis)

This is characterized by the spontaneous occurrence of abscesses in skeletal muscle. Pyogenic infection of skeletal muscle is rare in the West, but in the tropics it is one of the common outcomes of staphylococcal bacteremia.[10] The disease appears to have a predilection for children and adolescents, but it can occur in adults. Trauma and poor nutritional status are thought to be the predisposing factors in adults, but are not particularly significant in children.[10] Intravenous narcotic abuse has recently been associated with this complication.

Most cases of spontanteous bacterial myositis all over the world are caused by Staphylococcus aureus, although Staphylococcus albus and other organisms have occasionally been isolated.

The clinical features of this disease consist of localized muscle pain, followed in a few days by swelling, heat and tenderness, with or without fever and malaise. Local lymph nodes are usually not enlarged. Skin over the muscle abscess may be tight but is usually not edematous.[11] Blood cultures are generally negative by the time myositis occurs. The commonest site for pyomyositis is the thigh,[11] with buttock, arm, leg and groin

next.[10] Single abscesses are more frequent than multiple abscesses.

Treatment of spontaneous bacterial myositis includes surgical incision and drainage plus an appropriate parenteral antistaphylococcal antibiotic (methicillin, cephalothin). The mortality is low (approximately 1.4 per cent) but the condition can be fulminating.[11]

Synergistic Necrotizing Cellulitis

This disease is an aggressive soft tissue infection recently characterized by Stone and Martin.[12] The infectious process causes extensive necrosis of entire muscle compartments with little damage to the overlying skin and subcutaneous tissues and has associated severe systemic toxicity. There is a predilection for middle-aged and elderly persons in whom diabetes, renal disease and either obesity or malnutrition are present.

The disease results from a synergistic infection by one or more species of aerobic Gram-negative bacteria (Klebsiella, Enterobacter, Proteus mirabilis, Escherichia coli) and an anaerobe (anaerobic Streptococcus or Bacteroides or both).[12] It appears essential for both aerobic and anaerobic pathogens to be present for this extensive and rapid infection to occur.

The onset is acute and the incubation is variable, from three to 14 days. The infection is located primarily in the perineal area and the lower extremity. There are small skin ulcers draining copiously thin, reddish-brown, foul-smelling fluid referred to as "dishwater pus." There is exquisite local tenderness. The unique characteristic of this infection is discrete large skin areas of bluish-gray necrosis separated by areas of normal skin.[8] Some patients (25 percent) may have gaseous emphysema of adjacent tissues. Patients appear to be in a toxic condition although not all will be febrile. Uremia, anemia and ketoacidosis may be concommitant findings.

Diagnosis is made by doing a Gram stain of the exudate and identifying both Gram-positive cocci and Gram-negative rods. Blood specimens and the wound should be cultured both aerobically and anaerobically. There is a high incidence of associated aerobic and anaerobic bacteremia (30 percent).[12]

Therapy consists of radical surgical debridement and drainage in association with antibiotics to cover anaerobes (including B. fragilis) and bacillary Gram-negative aerobes. Clindamycin (600 mg given intravenously every six hours) and gentamicin (3 mg per kg of body weight per day in divided doses) are the antibiotics of choice. General supportive measures such as intravenous administration of fluids; correction of anemia, hyperglycemia and acidosis, and treatment of renal insufficiency are necessary. Mortality in this disease is high (75 percent).[12]

Necrotizing Fasciitis

Necrotizing fasciitis is a relatively rare, aggressive infection variably referred to as hemolytic streptococcal gangrene[13] and "hospital gangrene" in the older literature. The most significant manifestation of this infection is extensive necrosis of the superficial fascia with resultant widespread undermining of surrounding tissue and extreme systemic toxicity. Most cases occur following minor trauma or surgical procedures of the abdomen.[14,15] The highest incidence is seen in patients with ischemic small vessel disease, such as diabetes,[7] but it has also been noted in patients with neuropathies, urethral stricture, cirrhosis and heroin addiction.[16]

It was originally believed that aerobic organisms, particularly the hemolytic streptococci and staphylococci and Gram-negative bacilli, were the primary pathogens responsible for this infection.[13-15,17] However, with careful bacteriologic techniques the cause consistently has been shown to be polymicrobial, involving both anaerobes and aerobes.[16] The predominant anaerobes include Peptostreptococcus, Bacteroides, and Fusobacterium; the predominant aerobes include Escherichia coli, Proteus, Staphylococcus and Streptococcus.[16]

The disease is characterized by a rapid course. Initially there is pain (minimal) and swelling at the site of injury and the involved site becomes red, hot, swollen and edematous. Subsequently, there is hypoesthesia about the wound. The patient has a rapidly developing fever which may be preceded by a chill and is almost always followed by prostration.[13] The early swelling makes the skin tense, smooth and shiny with no sharp line of demarcation between normal and affected skin. As the disease progresses, there is a dusky discoloration of the skin appearing as small purplish patches with irregular or ill-defined borders.[14] At this time blisters or bullae appear in the affected area, and widespread echymoses and necrosis of the skin can occur. Sometimes the area of skin necrosis is very small, while the subcutaneous gangrene is quite extensive.[13] Pro-

nounced apathy and weakness develop in the patient. Hypocalcemia, due to extensive subcutaneous fat necrosis, anemia and jaundice may develop.[8,15] Blood is lost from the general circulation in venous thrombosis and cutaneous hyperemia, and there is sequestration of large quantities of extracellular fluid in the acutely inflamed areas. Lymphangitis or lymphadenopathy (or both) is very rare in this condition.[13]

Diagnosis is made by having a high index of suspicion and evidence of extensive subcutaneous and fascial necrosis with undermining of skin.[17] If there is an opening in the skin, a hemostat or probe may be readily passed through the opening along the fascial plane. In cellulitis or erysipelas without necrotic fascia, an instrument will not follow the subcutaneous plane.

The initial management should consist of correction of fluid and electrolyte abnormalities, blood transfusions as necessary, blood and wound cultures (aerobic and anaerobic) and Gram stain of the wound exudate. Intravenous administration of antibiotics should be started immediately after cultures are obtained and should be directed against potential pathogens depending on the site of infection and findings on Gram stain of the wound exudate. For cases secondary to surgical operation of the abdomen or rectum where mixed aerobic and anaerobic pathogens including Bacteroides fragilis are common, a combination of gentamicin and clindamycin or chloramphenicol is recommended.[7] It must be noted, however, that the primary treatment is prompt, extensive surgical incision, debridement and drainage of the affected areas. It is only through the use of surgical procedures that mortality of this devastating infection (approximately 30 percent) can be decreased.[15]

Progressive Bacterial Synergistic Gangrene

This disease produces a progressive spreading ulceration and necrosis of the skin and subcutaneous tissues, and usually results as a complication of intraabdominal surgical procedures.[18] It is a synergistic infection most commonly caused by a combination of anaerobic cocci and aerobic Gram-positive cocci or Gram-negative rods. This infection is also known as Meleney's synergistic gangrene.[19]

The progress of this infection is not rapid and is not associated with high fever or toxemia usually seen with other grave soft tissue infections. The infection is typically recognized at 10 to 14 days after the initial injury or operation and often starts around the suture line. The process may best be described as a slowly advancing, white subcutaneous slough.[18] The skin surrounding the wound becomes edematous, red and usually tender. With progression, a characteristic lesion results that is demarcated into three zones. There is a peripheral wide area of fiery red cellulitis around a zone of purplish tender skin. The central zone becomes necrotic and will ultimately ulcerate. The central ulceration results in undermining of the skin edges of the circumscribed lesion.[8] The most distressing symptom is the acute sensitivity of the wound, making dressing and all manipulations about the lesion extremely painful.

Gram stain of tissue sections or subcutaneous aspiration may show the causative organisms and guide the appropriate choice of initial antimicrobial therapy. Aerobic and anaerobic blood and wound cultures should be routinely obtained for microbial confirmation.

Surgical drainage and debridement (often of large areas) is the major treatment modality; however, antibiotics assume a primary role before surgical intervention. Antibiotics given at first should cover both aerobic Streptococcus and Staphylococcus. High dose penicillin and methicillin should be administered parenterally. If Gram-negative rods are seen on Gram stain, gentamicin and clindamycin or chloramphenicol should be used. The mortality rate from this infection continues to be high owing principally to delays in diagnosis and therapy.[2]

Decubitus Ulcers with Sepsis

Decubitus ulcers result from local ischemic lesions caused by prolonged compression of tissue with subsequent necrosis. Patients who are bedridden, for whatever cause, are prone to decubitus ulcers. Under-nutrition, low serum albumin, anemia and circulatory impairment add seriously to the hazard of this complication developing.[20]

A multitude of organisms (aerobic and anaerobic) have been isolated from infected decubitus ulcers. The aerobic organisms producing sepsis include Proteus, Escherichia coli, Enterobacter, Pseudomonas aeruginosa, Staphylococcus, Streptococcus, diphtheroids and yeast. Anaerobic isolates include Bacteroides (especially B. fragilis), Fusobacterium, Peptococcus, Peptostreptococcus, microaerophilic Streptococcus, Clostridium and

Eubacterium.[21-23] Of importance, is the evidence that bacteremia is frequently associated with infected decubitis ulcers and is commonly polymicrobial with a predominance of obligate anaerobes, particularly B. fragilis.[21-23]

In the serious form, patients present with fever, chills, hypotension and tachycardia or tachypnea, or both.[23] There is extensive tissue destruction with necrosis. Lesions may be foul-smelling with purulent drainage. Lesions are usually more extensive than physical findings would suggest and associated osteomyelitis is a common finding (40 percent).[23]

Gram stain of the exudate is not particularly helpful since a polymicrobial smear is expected. Cultures of the decubitus ulcer and blood (aerobic and anaerobic) are essential.

Management entails careful evaluation of the patient's condition and consideration of the decubitus ulcer as the source of sepsis. The most important treatment with this disease is surgical debridement. Initial antibiotic therapy should include either clindamycin or chloramphenicol for coverage of anaerobic bacteria, particularly Bacteroides fragilis. In addition, an aminoglycoside, such as gentamicin, should be administered to provide coverage for coliform organisms. General supportive measures, such as fluids given intravenously and vasopressor agents, are indicated. Mortality in this disease is high (48 percent).[23]

Human and Animal Bites

Infection following human or animal bites is common. Infection in human bites is almost always polymicrobial and usually consists of the endogenous oral flora (both aerobes and anaerobes). Pasteurella multocida is commonly isolated following domestic animal bites[24] and may be associated with septicemia, especially in cirrhotic patients.[25] Streptobacillus moniliformis and Spirillum minus are the two organisms implicated in rat bite fever.[26] All of the above organisms are sensitive to penicillin which is the drug of choice for infection secondary to a bite. In addition, excision of the wound, copious irrigation with sterile saline and immobilization are necessary for complete management.[8] In only rare instances should bite lesions be sutured.

Furunculosis and Cellulitis

Furunculosis or boils due to S. aureus, and impetigo and cellulitis due to S. aureus or group A streptococci are rarely emergency problems. However, there are at least three situations in which these infections may be potentially life-threatening: (1) infection around the face, (2) cellulitis in the presence of peripheral edema which renders the infection rapidly progressive and more difficult to treat and (3) local infection in the presence of immune deficiencies, especially leukopenia or leukemia.

When the infection is around the face, there is a risk of cavernous sinus thrombosis. Cavernous sinus thrombosis most frequently follows a nasal furuncle, but may occur with infection of the sinuses, teeth, eyes or ears. Cavernous sinus thrombosis should be considered in the differential diagnosis of any patient with periorbital edema. Important features to distinguish it from orbital cellulitis are involvement of the 3rd, 4th, 5th and 6th cranial nerves with a dilated pupil and fullness of retinal veins. Bacteremia will be present and meningitis may also develop. A history of manipulation of the nose, squeezing it, extracting hairs from it or incising furuncles around it is obtained in approximately a third of patients with cavernous sinus thrombosis.[27] Because of this, incising furuncles on the face has not been advised.[27] If drainage of lesions on the face is important, it is recommended that antibiotic therapy be instituted for 24 to 48 hours before the incision. Antibiotic therapy before incision may also be important in patients with immune deficiencies.

In patients with cellulitis it may be very difficult to obtain the responsible organism. Injection of sterile saline followed by needle aspiration at the edge of the lesion for appropriate culture may aid considerably in recovery of the causative pathogen.[28] Blood cultures should also be done. Because S. aureus and group A streptococci are the most likely pathogens, initial antimicrobial therapy to cover both these organisms is recommended until culture results are available. Penicillin is still the agent of choice for streptococci, while semisynthetic penicillins, such as methicillin, or cephalothin should be administered for staphylococcal disease.

Septic Arthritis

WILLIAM S. CRYAN, MD:* Infection of the joint space represents a medical emergency. Physicians evaluating patients who present with monoarticular arthritis must entertain a complete differential diagnosis that includes trauma, gout, pseudo-

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TABLE V-2.—*Septic Arthritis*

Predisposing Factors
Antecedent joint disease
Old age and debilitation
Steroids or immunosuppressive therapy
Diabetes, malignancy
Recent arthrocentesis
Gonococcal disease
Other Clues to Diagnosis
Shaking chills, leukocytosis, fever
Often monoarticular although gonorrhea may be initially migratory
Pronounced signs of inflammation

gout, hemarthrosis, intermittent hydroarthrosis and a variety of less common conditions. There is a primary responsibility, however, to rule out infection as a cause. Septic arthritis may have tragic consequences, resulting in lifelong loss of joint function. As an example, staphylococcal arthritis, if untreated, can lead to destruction and loss of function of a joint in a few days. Early diagnosis is of cardinal concern because this is, in the main, a curable disease.

The predisposing factors and other clues to diagnosis of septic arthritis are listed in Table V-2. The normal joint has a relatively high level of integrity, and spontaneous infection is the exception rather than the rule. In persons with altered host defense mechanisms, one sees an increased frequency of septic arthritis. This is particularly the case in a patient whose altered defense mechanisms are related to abnormal joint space integrity. It has been recognized now for a number of years that in patients with underlying joint disease, such as rheumatoid arthritis (RA), there is a pronounced increase in the frequency of infection in the already damaged joints.[29] What is unfortunate is that septic arthritis in such patients is frequently overlooked as simply another manifestation of RA.

This phenomenon can be shown simply in the following experimental model. If one injects Escherichia coli or other organisms into the blood stream of a rabbit, inducing a bacteremia, septic arthritis does not ensue, proving the general integrity of the joint space. However, a septic joint will develop if injection of the same concentration of bacteria into the rabbit's bloodstream is followed by traumatization of the joint (such as puncturing the joint with a sterile needle). Similarly a prosthetic device in the joint is a predisposing factor for development of septic arthritis.

It would also appear that generalized host resistance is important. For example, the debility of aged patients, the presence of an underlying malignancy, the use of immunosuppressive agents or the presence of certain unrelated systemic illnesses, such as sickle cell disease, may all increase the possibility of septic arthritis developing. In addition, a vigorous search should be made to locate any extra-articular infective focus that may be a potential source for bacteremia. As an illustration, in a patient in whom intermittent episodes of bacteremia occur, as in a person with active bacterial endocarditis, the chances of infective arthritis developing are increased.

Another underlying factor to consider is the sociologic milieu of the patient. Certainly those persons in their sexually active years are at greater risk than others to develop gonococcal (GC) arthritis. Similarly, a person addicted to intravenously taken drugs is subject to an increased frequency of septic arthritis, often in unusual sites with uncommon organisms.[30]

Although most infected joints result from blood-borne infection, direct involvement of a joint with a septic process may occur. This is seen in patients in whom there is interruption of the joint space integrity consequent to trauma, direct spread of infection from adjacent osteomyelitis or local extension to the sacroiliac or hip joints, such as seen in patients with inflammatory bowel disease.[31]

Synovial fluid analysis is strongly indicated in any patient with monoarticular or unexplained pauciarticular disease. The evaluation of the joint fluid can be of prime importance in the differential diagnosis of the arthritic disorder. Gross examination and a few simple laboratory tests can help characterize the fluid into three main groups as noted in Table V-3. Once the grouping of the fluid is established, the differential diagnosis will be narrowed considerably (see Table V-4). The immediate aim is to differentiate an infected joint from the other possible causes of monoarticular or pauciarticular arthritis.

The diagnosis of septic arthritis is somewhat more difficult when the less common joints are involved. Infection of the sternoclavicular or sternomandibular joints in users of intravenously taken drugs[30] and a septic hip joint in a patient with inflammatory bowel disease[31] are illustrative of this point. As an aside, a patient with a septic hip may present with a complaint of knee pain,

for in such cases pain is referred to the knee via the obdurator nerve. In these instances examination of the "affected" knee may be unrevealing and only a subtle swelling in the inguinal region may be noted. Joint aspiration under fluoroscopy may be necessary to confirm the diagnosis.

The types of organisms that may cause septic arthritis are varied. The frequency of specific organisms differs according to the patient population studied and the geographic area. Although almost any microorganism can cause infectious arthritis, the common bacterial agents are listed in Table V-5.

In general terms, children are somewhat prone to pyogenic infection and approximately 40 percent of septic arthritides in children are due to Staphylococcus aureus with pyogenic streptococcus causing about 25 percent. In infants from 7 months to 4 years old, Hemophilus influenzae is being increasingly recognized as a common etiological agent[32] and is probably as common as S. aureus. Gram-negative infection with coliforms accounts for 15 percent of such cases. Although Neisseria gonorrhoeae has been reported in children under ten years of age, it is distinctly uncommon.

In adult patients, there is a shift in the statistics, predominantly because of the notably higher incidence of GC arthritis.[33] In many series N. gonorrhoeae is the etiologic agent in greater than 50 percent of patients with septic arthritis. S. aureus (25 percent), pneumococcus, streptococcus and Gram-negative bacilli are then seen in roughly that order.

Although excellent reviews of gonococcal infections have been published,[33,34] a brief characterization of GC arthritis will be presented since it is such a common form of septic arthritis in adults. Somewhat greater than 80 percent of cases are seen in women, about half of whom are pregnant, menstruating or in the immediate postpartum period.[34] It is, in the main, a complication of

TABLE V-3.—*Differential Diagnosis by Joint Fluid Groups**

Group I (Noninflammatory)	*Group II (Inflammatory)*	*Group III (Septic)*	*Hemorrhagic*
Degenerative joint disease	Rheumatoid arthritis	Bacterial infections	Hemophilia or other hemorrhagic diathesis
Trauma†	Acute crystal-induced synovitis (gout and pseudogout)		Trauma with or without fracture
Osteochondritis dissecans	Reiter's syndrome		Neuropathic arthropathy
Osteochondromatosis	Ankylosing spondylitis		Pigmented villonodular synovitis
Neuropathic arthropathy†	Psoriatic arthritis		Synovioma
Subsiding or early inflammation	Arthritis accompanying ulcerative colitis and regional enteritis		Hemangioma and other benign neoplasm
Hypertrophic osteoarthropathy‡	Rheumatic fever‡		
Pigmented villonodular synovitis†	Systemic lupus erythematosus‡		
	Progressive systemic sclerosis (scleroderma)‡		

*From Rodnan GP, McEwen C, Wallace SL (Eds): Primer on the rheumatic diseases. JAMA 224:661-812(Suppl), Apr 30, 1973, Copyright 1973, American Medical Association.

†May be hemorrhagic.

‡Groups I or II.

TABLE V-4.—*Examination of Joint Fluid**

Measure	*Normal*	*Group I (Noninflammatory)*	*Group II (Inflammatory)*	*Group III Septic*
Volume (ml) (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque
Color	Clear	Yellow	Yellow to opalescent	Yellow to green
Viscosity	High	High	Low	Variable
WBC (per cu mm)	<200	200-2,000	2,000-100,000	>100,000†
Polymorphonuclear leukocytes	<25%	<25%	50% or more	75% or more†
Culture	Negative	Negative	Negative	Often positive
Mucin clot	Firm	Firm	Friable	Friable
Glucose (mg/100 ml)	Nearly equal to blood	Nearly equal to blood	>25, lower than blood	<25, much lower than blood

*From Rodnan GP, McEwen C, Wallace SL (Eds): Primer on the rheumatic diseases. JAMA 224:661-812(Suppl), Apr 30, 1973, Copyright 1973, American Medical Association.

†Lower with infections caused by partially treated or by low virulence organisms.

genital tract infection. The interval from onset of genitourinary infection to arthritis is extremely variable; however, the most common length of time between contact and symptoms is approximately one week. Frequently the onset of the disease is heralded by fever (in 80 percent) and in some circumstances with chills. Migratory arthralgias will then occur with variable signs of articular inflammation. It is during this early bacteremic phase that skin lesions are most commonly seen and occur in up to 50 percent of patients. Tenosynovitis of the wrist is a common concomitant finding. Classically, during the bacteremic stage, blood cultures may be positive, but if joint fluid is obtained it may be negative. A day or two later frank purulent arthritis develops in the same joint and class III joint fluid will be obtained. Culture of this fluid is often positive for the organism. The knees are most commonly involved, with ankles and wrists following.

In cases of suspected GC sepsis, it is wise to culture the pharynx and anus as well as genitalia, blood and synovial fluid. Other laboratory modalities tend to be of variable value, with about 60 percent of patients showing leukocytosis. Recently the use of fluorescent techniques has been reported in an attempt to show the presence of gonococcal antibodies, but these modalities are not yet in general use.

Septic arthritis with a pyogenic organism (other than GC) may cause rapid destruction of a joint.[35] Pyogenic arthritis tends not to be associated with migratory arthralgias, although fever and chills are not uncommon. The onset may be quite explosive, with the patient presenting with an exquisitely tender, red, swollen joint. Changes on x-ray studies may occur in a matter of days, with soft tissue swelling and patchy areas of osteoporosis appearing as a consequence of the intense hyperemia.

Infectious agents other than bacteria (see Table V-6) can produce a septic joint, and some of these present in a more insidious manner. Chief among these would be tuberculous arthritis.[36] The classic presentation of articular tuberculosis is a monoarthritis of subacute onset with pain, swelling and limitation of movement. Often the disease is seen in boys with the major weight bearing joints affected: the spine, hips and small bones of the feet. Often there are associated tuberculous lesions of other organs, such as pulmonary, genitourinary and so forth. Soft tissue swelling may be the only finding on an x-ray study but eventually the characteristic articular and cystic changes will be seen. Later, gross active destruction of bone occurs as is generally the case with other septic lesions of joints. There tends to be greater involvement of the distal bony structures. This is in contradistinction to the inflammatory arthritides, such as RA, in which proximal involvement is greater than distal. Cultures of synovial fluid for Mycobacterium tuberculosis may be negative and definitive diagnosis is best achieved through synovial biopsy. In the vertebral column there is a propensity for involvement in the thoracic area.[37,38] With characteristic paravertebral abscesses, the "steering wheel sign" is seen on x-ray studies, the ribs seeming to radiate out from a hub. The infective process involves the vertebral body above and below the joint space. This is different from metastatic disease due to cancer which initiates in the vertebral body and thus spares the vertebral body either above or below the lesion. Anterior collapse of the vertebral body may occur, leading to the classic gibbus deformity seen with Pott's disease. Antituberculous therapy with two drugs (that is, isoniazid and ethambutol) is indicated for this disease.

As has been mentioned, it is extremely important to make an early diagnosis of an infective arthritis. In general, it is best to admit such patients to hospital for a course of parenteral

TABLE V-5.—*Bacterial Organisms Causing Septic Arthritis*

Neisseria gonorrhoeae
Staphylococcus aureus
Hemophilus influenzae
Pneumococcus
Streptococcus
Bacteroides
Escherichia coli
Pseudomonas aeruginosa
Others

TABLE V-6.—*Infectious Arthritis*

Bacterial (pyogenic)
Viral
Rubella
After rubella vaccination
Mumps
Infectious hepatitis
Other
Tuberculous
Fungal
Mycoplasma
Syphilitic

antibiotics. Most antibiotic concentrations in the serum will be quickly reflected in the joint fluid and intraarticular installation of antibiotics is generally unnecessary. However, it is useful to repeat arthrocentesis in such patients because accumulation of leukocytes and debris in such a joint may continue to cause destruction. Therefore, repeated arthrocenteses are therapeutic. It is infrequently necessary to carry out orthopedic or open drainage of joints because it has been found that there is no functional improvement when open drainage of joints is done in contrast to medical needle aspirations.[39]

Antibiotic therapy is directed toward the specific suspected organism. In the patient with S. aureus, it is generally recommended that nafcillin (25 mg per kg of body weight every six hours) or methicillin (6 to 8 grams per day in divided doses) be employed. If antibiotic sensitivities show that the organism is penicillin-sensitive, then penicillin G at 50,000 to 70,000 units per kg of body weight every six hours should suffice. Continued therapy using oral administration for an additional four to six weeks may be required when S. aureus is the organism. For N. gonorrhoeae, penicillin G is the drug of choice at 5 to 10 million units per day given intravenously in divided doses. In younger patients, where Hemophilus influenzae may be involved, one can substitute ampicillin at 50 mg per kg of body weight every six hours. If a Gram-negative organism is suggested, then gentamicin (3 to 5 mg per kg body weight per day in divided doses) should be given until culture results are obtained.

Emergency Eye Infections

JOHN E. EDWARDS, JR., MD:* Almost any infection of the eye is a relative emergency. However, this discussion will be limited to six entities which have been chosen from the perspective of nonophthalmologists. This selection may differ somewhat from the choice of general ophthalmologists. For instance, mucormycosis (phycomycosis) is included, which is of particular significance to internists but is infrequently encountered by general ophthalmologists. The first three entities, acute bacterial conjunctivitis, dacrocystitis and corneal ulcer are usually definitively diagnosed and treated by ophthalmologists, but may present initially to a primary physician in the emergency department. The last three infections, orbital cellulitis, mucormycosis, and endophthalmitis, frequently involve the combined efforts of an opthalmologist and an internist for both diagnosis and systemic therapy. Before discussing these entities in detail, the normal flora of the eye will be reviewed.

Locatcher-Khorazo and Seegal[40] have summarized numerous studies of normal eye flora which show the most common organisms cultured from uninfected eyes to be Staphylococcus aureus, Staphylococcus epidermidis and diphtheroids. A small percentage of normal patients harbor Gram-negative rods, including Pseudomonas aeruginosa. The presence of these Gram-negative rods should alert a physician to the necessity of giving adequate antibiotic coverage for these organisms when it is necessary to begin treatment for a severe infection without a specific diagnosis.

Fortunately, numerous antibiotics are capable of penetrating the eyes. Leopold and Kagan[41] have summarized these data and formulated a table outlining the potential for penetration into eye structures (see Table V-7). The routes for administration of antibiotics in eye infections include topical, subconjunctival, sub-Tenon and parenteral. The different clinical situations dictate the desired route of administration and will be discussed below.

Acute Bacterial Conjunctivitis

The clinical diagnosis of acute conjunctivitis usually does not create a diagnostic dilemma; however, one must not overlook an underlying panophthalmitis, associated orbital cellulitis, ocular trauma, foreign body or other primary intraocular processes. Locatcher-Khorazo and co-workers[42] reviewed the microbiology of 8,068 cases of acute bacterial conjunctivitis seen at the Institute of Ophthalmology, Columbia-Presbyterian Medical Center, between 1938 and 1968. In adults, Streptococcus pneumoniae, Hemophilus influenzae and S. aureus were the most common organisms. In children (up to 18 years old) S. pneumoniae and H. influenzae were still the most common organisms, followed by Streptococcus viridans and S. aureus. As expected, Neisseria gonorrhoeae played an important role in term babies. With the rising incidence of gonorrhea infections in this country, this organism should be kept relatively high in the differential diagnosis. Some cases have now been re-

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TABLE V-7.—*Intraocular Penetration of Antibiotics**

Relatively Good	*Fair*	*Poor*
Ampicillin	Colistin	Amphotericin
Cephalexin	Erythromycin	Novobiocin
Cephaloridine	Gentamicin	Oxacillin
Cephalothin	Kanamycin	Ristocetin
Chloramphenical	Methicillin	Streptomycin
Dicloxacillin	Neomycin	Tetracycline
Lincomycin	Oleandomycin	
	Penicillin	
	Polymyxin	
	Vancomycin	

Note: Those antibiotics with fair penetration are able to penetrate the inflamed eye in therapeutic concentrations against many organisms.

*From Leopold IH, Kagan JM: Antimicrobial therapy in ophthalmology, chap 40, *In* Kagan BS (Ed): Antimicrobial Therapy, 2nd Ed. Philadephia, W. B. Saunders Co., 1974, p 371

ported in association with disseminated gonorrhea in adults.[43]

Generally, it is possible to identify the specific agent by Gram stain and culture of the involved area. A swab of the infected conjunctiva will obtain appropriate material. Treatment is usually successful with a topical antibiotic (either sulfonamide or tetracycline). Although agents containing neomycin and polymyxin have been popular for years, recent evidence suggests that a significant percentage of pneumococcal organisms may be relatively resistant to these constituents.[44]

Acute Dacrocystitis

This disease is an inflammation of the nasal lacrimal ducts. By far the most common etiological agent is S. aureus, with S. pneumoniae second.[42] Nocardia is another organism that, surprisingly, has been frequently cultured from this infection and should be kept in the differential diagnosis. The most common complication of dacrocystitis is pneumococcal corneal ulcers. Optimal therapy consists of parenteral antistaphylococcal antibiotics and warm compresses. Additionally, this infection is almost always associated with obstruction of the lacrimal duct, which must be relieved to assure adequate healing.

Corneal Ulcers

When present in the relatively advanced stage, a corneal ulcer can be easily diagnosed by nonophthalmologists without the aid of specialized instrumentation. The definitive microbial diagnosis, however, is usually made by smear and culture of the base of the ulcer. The scraping of the ulcer base is best done by an experienced ophthalmologist. S. aureus, S. pneumoniae and P. aeruginosa are the most common organisms.[42] With the possible exception of the herpetic corneal ulcer, which has a dendritic configuration, one cannot make a clinical distinction between ulcers caused by other microbial agents.

The usual mode of treatment of the corneal ulcer is topical antibiotics. However, if there is extensive clouding of the cornea and anterior chamber inflammation suggestive of intraocular penetration, systemic antibiotics are required in addition. Because of the relatively high incidence of Pseudomonas and its potential for aggressive destruction (it may cause loss of the eye in 48 hours), appropriate coverage for this organism should be given when smear of the ulcer base suggests its presence. A topical ointment containing polymyxin in addition to subconjunctival and systemic gentamicin should be used.

This brings us to the three ocular inflammations which are most likely to require the combined efforts of the internist and ophthalmologist in both diagnosis and management.

Orbital Cellulitis

This disease is a severe, potentially lethal infection which may be accompanied by septic shock or cavernous sinus thrombosis, or both. The process is usually secondary to sinusitis, trauma, conjunctivitis, dacrocystitis or hemotogenous seeding from a remote source. Obviously, aggressive efforts should be extended to locate a primary source for the infection. Orbital cellulitis must also be differentiated from numerous other entities which may resemble an acute infection such as tuberculosis, syphilis, anthrax, sarcoidosis, Wegener's granulomatosis, phycomycosis, aspergillosis, lethal midline granuloma, xanthoma and inflammatory pseudotumor of the orbit.[45]

The most common organisms causing bacterial orbital cellulitis are S. aureus, S. pneumoniae, S. viridans and hemolytic streptococci.[42] However, Gram-negative rods, including Pseudomonas, have also been implicated. With the rising incidence of penicillin-resistant staphylococci an antibiotic, such as methicillin or cephalothin, in combination with gentamicin should be used for initial coverage. The complications of orbital cellulitis include cavernous sinus thrombosis, meningitis, dacrosystitis, severe lid scarring and panophthalmitis. If the initial antibiotic treatment is ineffective, the most fluctuant area of involve-

ment must be drained. Bacterial diagnosis should be attempted with needle aspiration of the involved area and Gram stain and culture. The advancing margin of the inflammatory area should be aspirated. Addition of warm compresses to the area of involvement may be beneficial.

Mucormycosis (Phycomycosis)

This infection almost always occurs in a setting of severe debilitation or diabetes. When associated with diabetes, ketoacidosis is usually present. The disease generally presents as a unilateral orbital infection associated with ophthalmoplegia and proptosis. It can result from either hematogenous spread or direct extension from the nasal sinuses. A black crusting material may accompany the exudate either around the eye or exuding from the nares. The specific diagnosis can usually be made by scraping the lesion and identifying the broad based nonseptate hyphae by direct microscopic examination. If material cannot be obtained directly from the eye, a swab of the nose should be examined.

The complications of this disease are devastating and the fatality rate approaches 90 percent. The most important complication is cavernous sinus thrombosis with subsequent intracerebral infection. The treatment of choice is systemic amphotericin B. Any patient presenting with orbital mucormycosis should have careful evaluation for the presence of infection elsewhere, particularly in the central nervous system, lung and gastrointestinal tract.[46] Further characterization of this infection is presented elsewhere in the symposium (see Part I).

Endophthalmitis

Generally, endophthalmitis occurs following surgical operation on the eye. Therefore, an ophthalmologist is usually the primary physician making the diagnosis in this situation. However, another important cause of endophthalmitis is hematogenous seeding of the eye and frequently a nonophthalmologist is the first physician to suspect this diagnosis. Hematogenous endophthalmitis may be a complication of infective endocarditis as exemplified by recent reports of endophthalmitis associated with staphylococcal endocarditis.[47] S. aureus is the most common cause of endophthalmitis with P. aeruginosa second. Because of the presence of the two organisms, use of an antistaphylococcal agent, such as methicillin, plus gentamicin should be used systemically for initial coverage. If a patient is allergic to penicillin then cephalothin or vancomycin may be substituted. In addition to the systemic route, the gentamicin should be given topically or subconjunctivally.

Recently a number of reports have emphasized the importance of fungal and fungal-like agents causing endophthalmitis. Probably the most common of these organisms is Candida.[48,49] These organisms not only can cause destructive ocular disease but also may be important clues to underlying disseminated mycosis. This type of endophthlamitis is best treated with systemic amphotericin B. 5-Fluorocytosine, either alone or in combination with amphotericin B, may prove to be an important agent as further clinical experience is accumulated.

These six eye diseases represent infectious emergencies and may result in permanent loss of vision and even death. Avoidance of these complications depends upon early diagnosis and early institution of appropriate therapy. Because of the high incidence of staphylococcal infection in the eyes and the potential for rapid ocular tissue destruction with Gram-negative rods, which are occasionally encountered, broad spectrum antibiotics should include agents effective against penicillinase-producing staphylococci and Gram-negative rods, primarily Pseudomonas. The toxicity of these antibiotics must be monitored carefully when given systemically.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Chloromycetin®	*chloramphenical*
Keflin®	*cephalothin*
Cleocin®	*clindamycin*
Garamycin®	*gentamicin*
INH®, Triniod®, Nydazid®	*isoniazid*
Myambutol®	*ethambutol*
Polycillin®, Omnipen®, Tocacillin®, Amcil®, Penbritin®, Principen®	*ampicillin*
Unipen®	*nafcillin*
Staphcillin®	*methicillin sodium*
Sulfonamide	*sulfonamide*
Anchromycin®, Panmycin®, Tetracyn®	*tetracycline HCl*
Mycifradin sulfate®	*neomycin*
Polymyxin B sulfate®	*polymyxin B sulfate*
Fungizone®	*amphotericin B*
Prostaphlin®	*oxacillin*
Vancocin®	*vancomycin*
Ancobon®	*5-fluorocytosine*
Keflex®	*cephalexin monohydrate*
Loridine®	*cephaloridine*
Dynapen® Pathocil® Veracillin®	*dicloxacillin*
Lincocin®	*lincomycin hydrochloride monohydrate*

Coly-Mycin S® ..... *colistin sulfate*
E-Mycin®, Erythrocin®, Kesso-Mycin®, Ilotycin®, Robimycin®, Pediamycin® ..... *erythromycin*
Kantrex® ..... *kanamycin*
Cyclamycin®, Tao® ..... *oleandomycin*
Albamycin® ..... *novobiocin*
Ristocetin ..... *ristocetin*
Streptomycin ..... *streptomycin*

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